

Joint UNAIDS -UNICEF SD- WHO/EDM Project

Essential drugs used in the care of people living with HIV: sources and prices.

February 2000

Introduction

Treatment for HIV-related conditions is limited in developing countries. Explanations include limitations in their diagnosis and treatment infrastructure, lack of epidemiological data on the patterns of opportunistic diseases that is necessary to plan treatment interventions, gaps in their supply system, and the high cost and poor ability to finance the purchase of drugs. To improve access to drugs used in HIV-related conditions, the WHO Expert Committee on the Use of Essential Drugs included in the tenth and eleventh Model List of Essential Drugs a number of drugs used to treat opportunistic infections of special importance in HIV/AIDS. However, most of them were not included in the range of products distributed by international generics suppliers, and access to them remained limited in developing countries. The availability of price information comparison for these drugs was also very limited.

To find supply solutions for those drugs UNAIDS, UNICEF and WHO initiated a joint project that specifically sought to identify suppliers and supply-related information for them. The outcome of this project has been a database containing information relevant to drug procurement that could be used by countries and donors to improve access to HIV-related drugs. The project did not intend to assess and pre-qualify suppliers: procurement agencies should follow their own procedures in this respect.

Drug selection and sources

The products included in the project were 22 active ingredients, present in 44 pharmaceutical presentations. They included essential drugs used to treat opportunistic infections and HIV-related malignancies, in the prevention of mother to child transmission and in palliative care. Fluconazole, itraconazole and methadone, were included due to their relevance to people with HIV infection. In December 1999, fluconazole was added to the Model List of Essential Drugs, replacing ketoconazole.

Over two hundred companies from a total of 40 countries which had products licensed in their respective countries were contacted. One third of these replied with information. The information requested included: registration status of the product in the country of origin, information on production capacity and lead times, indicative prices in

origin and possession of manufacturing license and GMP certificate issued by their respective National Drug Authorities.

While all attempts were made to contact as many manufacturers as possible, the list remains incomplete and is open to further additions. Additionally, some drugs are the subjects of patents in some countries, precluding the introduction of generic alternatives to them in those countries. This matter is country specific and must be addressed at National level.

Supply and Prices

The data collected during the study shows that the majority of drugs are available on the international market. Prices vary widely, but realistic indicative prices for bulk procurement can be estimated for many products. The limitations of these 'indicative' prices are:

- a) Prices apply generally in the context of bulk procurement i.e. the working unit is one batch. Batch sizes vary greatly among formulations and manufacturers, but the following sizes were the more typical: capsules and tablets, 100000 to 500000 (batches of over 1 million not uncommon, but these are not minimum purchases); vials and bottles, 5000 to 20000.
- b) Prices are ex-works or FOB. Freight, insurance and taxes are not included.
- c) Manufacturers may have contractual agreements or different pricing structures for specific countries. These factors were not included in the study.

In most cases, these indicative prices are a fraction of prices often used in comparisons, such as those published in the British National Formulary.

The following information is provided for each drug:

- 1- General comments on availability and cost.
- 2- Inclusion in the WHO Model List of Essential Drugs (11th revision December 1999).
- 3- For each therapeutic class, price of drugs (with their range, median, and 25th percentile of the price distribution), as supplied by their manufacturers, the number of manufacturers that gave indicative prices, and, for comparison, two list prices from the UK and Spain. For these two list prices the lower bioequivalent products are shown, with no differentiation between original or generic products. The difference in costs of drugs between the British and the 25th percentile price taken from the survey is added for examples of HIV-related conditions. This illustrates the potential of using the information gathered in this survey.

Further information and contacts.

Outputs of the database include: (a) product information related to availability, cost and shelf life, (b) range of indicative prices of individual products, with examples of established and publicly available tender prices (if available) and (c) manufacturer contact information. Parts (a) and (b) are published in the internet and will be updated as new information is collected. Contact information of manufacturers can be supplied to

government agencies and purchasing groups on request. Manufacturers interested in supplying information are also invited to contact the project.

1- DRUGS USED TO TREAT OPPORTUNISTIC INFECTIONS AND FOR PREVENTION OF MOTHER TO CHILD TRANSMISSION

1.1- ANTIBACTERIAL DRUGS

Ceftriaxone, Ciprofloxacin, Clindamycin, Sulfadiazine

Ceftriaxone

Ceftriaxone was added to the WHO Model List of Essential Drugs (EDL) in 1995 as a reserve antibacterial. It is an important drug used in the treatment of sexually transmitted diseases and bacterial meningitis. However, its high price is an obstacle to accessing this drug (this applies also to other third generation cephalosporins).

In 1999, alternatives to the original product (Rocephin®, manufactured by Hoffman-La Roche) were marketed at least in the following countries: Argentina, Brazil, Cameroon, Cambodia, China, Greece, India, Kenya, Syria, Malawi, Mexico, Myanmar, Slovenia, South Africa, Spain, Sri Lanka, Tanzania, Taiwan, Thailand, Trinidad, Uganda and Vietnam. Despite the expiry of the original patent in 1999 (US and European patents), additional protections prevent the introduction of generics in many countries. Generic ceftriaxone products can be considerably cheaper than the patented product.

Use in HIV/AIDS: Sexually Transmitted Diseases (STD).

Notes in 11th Model list: Example of therapeutic group. Reserve antimicrobial. To be used only when there is significant resistance to other drugs on the list.

- **powder for injection, 250 mg (as sodium salt) in vial.** EDL. Reported shelf-life: 36 months.

Ciprofloxacin

This broad-spectrum antimicrobial is included in the EDL as an example of therapeutic group (quinolones). It was added to the seventh list (1991) as a complementary antimicrobial to be used only in patients with infections resistant to other drugs in the List. In the ninth list (1995), it was transferred to the main list. While it is accepted that wide use of fluoroquinolones is not advisable due to development of resistance, the high price of ciprofloxacin is an obstacle to its utilisation when it is needed.

Patented by Bayer in 1981 (Germany), ciprofloxacin has been available from other manufacturers in markets where product patents are not applicable. Prices of generics for bulk procurement vary among manufacturers and countries, but in the great majority of cases these are much lower than that of the patented product in western markets. Most of the manufacturers that replied had carried out bioequivalence studies.

Use in HIV/AIDS: Treatment of bacterial infections, including salmonellosis and shigellosis. STD protocols.

Notes in 11th Model list: Example of therapeutic group.

- **tablets, 250 mg.** EDL. Reported shelf-life: 24 to 36 months.

Clindamycin

Clindamycin injection was added to the EDL in 1991 as a complimentary drug for use in patients allergic to penicillin and in infections resistant to other drugs in the main list. The capsules were added in 1997. The generic market for clindamycin is not very extended.

Use in HIV/AIDS: Treatment of PCP, treatment of toxoplasmosis.

Notes in 11th Model list: Complementary drug (when drugs in the main list are known to be ineffective or inappropriate for a given individual). Limited indications or spectrum of activity.

- **capsule, 150 mg.** EDL. Reported shelf-life: 36 months.
- **injection, 150 mg(as phosphate)/ml.** Available in 2, 4 and 6 ml ampoules. EDL. Reported shelf-life: 24 months.

Sulfadiazine

Sulfadiazine, developed in 1940, was added in 1997 to the EDL. Its inclusion, replacing sulfadimidine, was on the basis of its efficacy in the treatment of toxoplasmosis in combination with pyrimethamine. It is included in the list representing short-acting systemically-acting sulfonamides.

Largely an abandoned drug, it received renewed attention for the treatment of cerebral toxoplasmosis in AIDS patients. In 1992 there was a shortage of the drug in the US, as the only manufacturer ceased operations. In 1994, it was reintroduced in the market with orphan drug status, carrying a seven year period of exclusivity. In the US, the AWP in 1991 was 3.10 USD for a pack of 100 tablets, but today the drug is 30 times more expensive (AWP 98.73 USD/pack).

Sulfadiazine sodium injection is marketed in few countries, and its price is very high. Only one manufacturer was identified.

The combination sulfadiazine-pyrimethamine-calcium folinate is considered as a first line treatment for cerebral toxoplasmosis. Treatment costs associated with this combination can vary widely depending on the price of any of the drugs (specially sulfadiazine and calcium folinate). An example of costs is presented in the description of antipneumocystosis and antitoxoplasmosis drugs (table 8).

Use in HIV/AIDS: Treatment of toxoplasmic encephalitis and other manifestations of active toxoplasmosis.

Notes in 11th Model list: Example of therapeutic group. In renal insufficiency, contraindicated or dosage adjustments necessary.

- **tablets, 500 mg.** EDL. Reported shelf-life: 48 to 60 months.
- **injection, 250 mg (sodium salt) in 4-ml amp.** EDL.

Table 1. Sources and prices of antibacterial drugs.

ANTIBACTERIALS	Manuf. (1)		Indicative prices (USD, 1999) (2)						List Prices (3)	
	No./countries		Unit	MAX	MIN	MEDIAN	25th Perc./No.<		UK	Spain
Ceftriaxone										
inj, 250 mg in vial	5	5	vial	2.24	0.29	1.55	1.00	2	4.62	2.31
Ciprofloxacin										
tab, 250 mg	14	7	tab	0.95	0.02	0.09	0.03	4	1.21	0.56
Clindamycin										
capsule, 150 mg	3	3	cap	0.15	0.05	0.08	0.06	1	0.77	0.10
inj, 150 mg/ml in amp	1	1	2-ml	0.38	0.38	0.38	0.38	1	8.32	1.77
Sulfadiazine										
inj, 250 mg in 4-ml amp.	1	1	amp	7.89	7.89	7.89	7.89	1	7.99	----
tab, 500 mg	6	6	tab	0.77	0.03	0.18	0.06	2	0.45	0.07

Explanatory notes to tables at the end of the document

1.2- ANTIFUNGAL DRUGS

Amphotericin B, Fluconazole, Itraconazole, Ketoconazole

Amphotericin B

Amphotericin B is marketed worldwide by Bristol Myers Squibb. It is an essential drug for the treatment of cryptococcal meningitis and other life-threatening infections that affect people living with HIV. Although Amphotericin B is an old drug, its manufacture is difficult. This, together with the preference in developed markets of less toxic lipid-based formulations, has prevented wide generic competition. It is an expensive drug, also in developing countries.

Use in HIV/AIDS: Cryptococcal meningitis, histoplasmosis and coccidioidomycosis, aspergillosis.

Notes in 11th Model list: In renal insufficiency, contraindicated or dosage adjustment necessary.

- **powder for injection, 50 mg in vial.** EDL. Reported shelf-life: 24 months, REFRIGERATION REQUIRED.

Fluconazole

Introduced in the 11th Model EDL, fluconazole represents the group of triazole antifungal drugs. It replaced ketoconazole.

Pfizer holds the patents for this important fungicide, and the company's price policy has attracted a great deal of attention. In the US, the patent expires on January 2004 (the patent expired originally in 2001 but the protection period was extended). The British and European patents were granted in late-1981 and January 1982. Fluconazole has also been at the centre of the market exclusivity/compulsory license debate, especially in relation to Thailand (where generic alternatives are now available) and South Africa (where it is still under patent).

Presently, fluconazole capsules, tablets and solution for injection are produced by generic manufacturers in numerous countries where no product patent protection exists. The indicative price of some of these drugs is many times lower than the patented product. No generic manufacturers of oral suspension were found, and therefore no prices are indicated.

Use in HIV/AIDS: Treatment and prophylaxis of cryptococcal meningitis, treatment of oesophageal and resistant oropharyngeal candidiasis and vaginal candidiasis, treatment and maintenance of coccidioidomycosis.

Notes in 11th Model list: Example of therapeutic group.

- **capsule, 50 mg. EDL.** Reported shelf-life: 24 to 36 months.
- **capsule/tablet, 150 mg.** Strength not in EDL. Reported shelf-life: 24 to 36 months.
- **capsule/tablet, 200 mg.** Strength not in EDL. Reported shelf-life: 24 to 36 months.
- **solution for injection, 2 mg/ml in bottle.** EDL. Reported shelf-life: 24 to 36 months.
- **oral suspension, 50 mg/5-ml.** EDL.

Itraconazole

Itraconazole is important in the treatment of certain fungal infections related to HIV/AIDS. The new revision of the list (1999) includes as an essential drug fluconazole, a member of the same family (triazoles). Itraconazole is marketed in most countries only as a proprietary product and limited sources of generics exist. Prices indicated by two generic manufacturers were significantly cheaper than the lowest list price found of the original product (price in Spain of Sporanox®, Janssen-Cilag). No generic producers of the oral solution were found.

Itraconazole is mainly patented in industrialized countries. The patent will expire soon in countries where no extensions have been given (original US and European patents filed between 1979 and 1980).

Use in HIV/AIDS: Treatment of resistant oral and oesophageal candidiasis, maintenance of cryptococcosis, treatment of histoplasmosis.

- **capsule, 100 mg.** Not in EDL. Therapeutic group represented by fluconazole. Reported shelf-life: 36 months.
- **oral solution, 10 mg/ml.** Not in EDL.

Ketoconazole

Ketoconazole was included in the 10th Model EDL, but it has been replaced in the last revision by fluconazole, which has a better therapeutic profile and reduced hepatic toxicity.

The tablet form is available as generic in most markets. It is offered by international distributors and it is also included in the UNICEF list.

Use in HIV/AIDS: Treatment of oesophageal and resistant oropharyngeal candidiasis.

- **tablet, 200 mg.** EDL Reported shelf-life: 36 months.
- **oral suspension, 100 mg/5ml.** EDL.

Table 2. Sources and prices of antifungal drugs

ANTIFUNGALS	Manuf. (1)		Indicative prices (USD, 1999) (2)						List Prices (3)	
	No./countries		Unit	MAX	MIN	MEDIAN	25th Perc./No.<		UK	Spain
Amphotericine B										
inj, 50 mg in vial	----	----	vial	----	----	----	----	----	5.94	2.47
Fluconazole										
cap/tab, 50 mg	2	2	cap/tab	0.12	0.04	0.08	0.06	1	3.82	1.72
cap/tab, 150 mg	2	2	cap/tab	0.29	0.12	0.21	0.16	1	11.45	5.23
cap/tab, 200 mg	4	2	cap/tab	7.25	0.15	0.62	0.23	1	15.26	6.71
inj, 2mg/ml	3	2	100-ml	9.50	0.45	1.75	1.10	1	47.10	8.93
Itraconazole										
cap, 100 mg	2	2	cap	0.54	0.30	0.42	0.36	1	2.41	1.26
oral solution, 10 mg/ml	----	----	150-ml	----	----	----	----	----	84.09	52.18
Ketoconazole										
tab, 200 mg	9	8	tab	0.32	0.05	0.11	0.09	3	0.84	0.29

Explanatory notes to tables at the end of the document

Table 3. Drug cost associated with the treatment of cryptococcosis.

CRYPTOCOCCOSIS. Treatment and duration (4)						Project estimates (25th percentile)		United Kingdom	
Drug	unit	Daily Dose	units/day	Days	Total units	Unit price (USD)	Total	Unit price (USD)	Total
Treatment									
Amphotericine B	inj 50 mg	0.8 mg/Kg	1	14	14	2.47 (a)	35	5.94	83
followed by fluconazole	cap 200 mg	400 mg	2	56	112	0.23	26	15.24	1707
							61		1790
Secondary prophylaxis									
fluconazole	cap 200 mg	200 mg	1	365	365	0.23	84	15.24	5563

Explanatory notes to tables at the end of the document

(a)- Manufacturer list price in Spain. No price was supplied by manufacturers.

1.3- ANTIVIRAL DRUGS

Aciclovir, Zidovudine, Nevirapine

Aciclovir

Aciclovir and zidovudine were the first antivirals added to the EDL. Aciclovir was incorporated to the list in 1997, in the therapeutic category of antiherpes. It has a very important role in HIV and STD for the treatment of severe primary genital herpes, disseminated herpes zoster and herpes encephalitis.

Patent expiry has opened up the market and the cost of a once very expensive drug has decreased considerably. Prices vary among different markets. There are numerous manufacturers of tablets, many with studies of bioequivalence to the original product. Indicated shelf-life varies among products. It was recently included in the list of an international distributor. Dispersible tablets have generally a shorter shelf life than the tablet form and are more expensive. The majority of products on the market are tablets, and no distinction was made when comparing products. Aciclovir powder for injection, used in hospital settings for treatment of herpes encephalitis, is not as widely available as the tablet form. However, a number of generic products exist.

Use in HIV/AIDS: Severe primary genital herpes, disseminated herpes zoster and herpes encephalitis

Notes in 11th Model list: Limited indications or narrow spectrum of activity.

- **powder for injection, 250 mg (as sodium salt).** EDL. Reported shelf-life: 24 to 60 months.
- **tablet, 200 mg.** EDL. Reported shelf-life: 24 to 60 months.
- **tablet, 800 mg.** Strenght not in EDL Reported shelf-life: 24 to 60 months.

Table 4. Sources and prices of antiviral (antiherpes) drugs.

ANTIVIRALS	Manuf. (1)		Indicative prices (USD, 1999) (2)						List Prices (3)	
<i>Antiherpes</i>	No./countries		Unit	MAX	MIN	MEDIAN	25th Perc./No.<		UK	Spain
Aciclovir										
inj, 250 mg	10	9	vial	18.90	1.74	3.73	2.62	3	17.55	4.68
tab, 200 mg	18	15	tab	0.76	0.04	0.11	0.07	5	0.39	0.68
tab, 800 mg	10	9	tab	1.55	0.20	0.40	0.26	3	0.73	2.12

Explanatory notes to tables at the end of the document

Table 5. Drug cost associated with the treatment of herpes simplex.

HERPES SIMPLEX. Treatment and duration (4)						Project estimates (25th percentile)		United Kingdom	
Drug	unit	Daily Dose	units/day	Days	Total units	Unit price (USD)	Total	Unit price (USD)	Total
Treatment									
Acyclovir	tab 200 mg	1000 mg	5	5	25	0.07	2	0.39	10

Explanatory notes to tables at the end of the document

Zidovudine (AZT)

Zidovudine was added to the tenth EDL for the only indication of prevention or reduction of mother-to-child transmission. The drug is at the center of a political pricing/access debate, and several groups have carried out studies on availability of generics, pricing and trade matters. Generic versions are widely available, as 100 mg and 250 mg capsules. The dosage used in prevention of MTCT is usually 300 mg. Countries where generic zidovudine is marketed include Argentina, Brazil, Canada, Chile, Costa Rica, Czech Republic, Guatemala, Honduras, India, Iraq, Cote d'Ivoire, Jamaica, Mexico, Panama, Singapore, Tunisia, Venezuela, Slovak Republic, Spain, Sri Lanka and Thailand.

Indicative prices vary widely depending on the country of origin of the product. Present tender price in Brazil is 0.20 USD per 100 mg cap (three manufacturers, 1999).

Use in HIV/AIDS: Prevention of Mother to Child Transmission.

Notes in 11th Model list: Limited indications or narrow spectrum of activity.

- **capsule, 100 mg.** EDL. Reported shelf-life: 24 to 60 months
- **capsule, 250 mg.** EDL. Reported shelf-life: 48 to 60 months
- **injection, 10 mg/ml in 20-ml vial.** EDL. Reported shelf-life: 12 months
- **oral solution, 50 mg/5-ml.** EDL. Reported shelf-life: 18 to 24 months
- **tablet, 300 mg.** Non-EDL. Used in pilot projects for prevention of MTCT. Provided as a donation by the manufacturer to a restricted number of countries.

Table 6. Sources and prices of antiviral (antiretroviral) drugs.

Antiretrovirals	Manuf. (1)		Indicative prices (USD, 1999) (2)						List Prices (3)	
	No./countries		Unit	MAX	MIN	MEDIAN	25th Perc./No.<		UK	Spain
Zidovudine (AZT)										
capsule, 100 mg	6	4	cap	0.55	0.27	0.40	0.29	2	2.01	0.75
capsule, 250 mg	4	3	cap	1.92	0.68	0.86	0.73	1	----	1.68
oral solution, 50 mg/5-ml	2	2	vial	17.62	6.90	12.26	9.58	1	40.20	19.89

Explanatory notes to tables at the end of the document

Nevirapine

This drug, used in combination therapy in HIV, was included in the last revision of the Model List for the same indication as zidovudine (prevention of mother-to-child transmission).

For this indication, a combination of tablet for the mother and syrup formulation for the newborn child is required. The indicative cost per treatment is 4 USD from the patent holder.

Nevirapine is a recently introduced drug and therefore patent-protected in many countries. However, it might not be patented in most developing countries. Tender and negotiated prices of the proprietary product vary from 2 USD to 4 USD for the 200 mg tablet. There are at least three generic manufacturers in Brazil.

1.4- ANTIPROTOZOALS. ANTIPNEUMOCYSTIS AND ANTITOXOPLASMOSIS DRUGS.

Pentamidine, Pyrimethamine, Calcium Folate (cytotoxic)

Pentamidine

To address the increasing problem of toxoplasmosis and infection with *Pneumocystis carinii* in immunosuppressed patients, the tenth EDL incorporated a new section dedicated to these agents. This section included pentamidine isethionate, pyrimethamine and sulfamethoxazole+trimethoprim. Pentamidine isethionate was previously included in the list as an antitrypanosomal drug (in 200 mg strength). The new strength included, 300 mg, is available from at least five manufacturers. Two presentations exist, powder for injection and nebuliser. The 200 mg presentation is offered only by Rhone Poulenc, and is available through WHO for trypanosomiasis programmes.

Use in HIV/AIDS: Prophylaxis of *Pneumocystis carinii* pneumonia, treatment of *Pneumocystis carinii* pneumonia in patients unable to tolerate first-line treatment.

Notes in 11th Model list: Specific expertise, diagnostic precision, individualization of dosage or special equipment required for proper use.

- **powder for injection, 200 mg (isetionate) in vial.** EDL.
- **powder for injection, 300 mg (isetionate) in vial.** EDL. Reported shelf-life: 18 to 60 months.

Pyrimethamine

Pyrimethamine is an essential component of treatment regimes against *Toxoplasma gondii*. Pyrimethamine is available as generic from international suppliers and as branded product (Glaxo Wellcome). While generic pyrimethamine tablets are available at a low cost, they are used in combination with calcium folinate (to reduce its toxicity) and sulfadiazine or clindamycin, and therefore adequate access to these drugs must be also ensure.

Use in HIV/AIDS: Treatment of toxoplasmic encephalitis and other manifestations of active toxoplasmosis, treatment of isosporidosis.

- **tablets, 25 mg.** EDL.

Calcium Folate (Cytotoxic drug)

Calcium folinate is included in the EDL as cytotoxic drug. However, it is an essential drug for the treatment and prophylaxis of toxoplasmosis, where it is used to reduce the toxicity of pyrimethamine. It is considered an expensive drug, and its price is a critical factor in the total drug cost of toxoplasmosis management.

Originally a product of Wyeth-Lederle, calcium folinate in tablets is available as generic. While indicative prices varied widely, low cost sources were found. One international supplier offers it.

Use in HIV/AIDS: To decrease the toxicity of pyrimethamine and other inhibitors of folic acid.

Notes in 11th Model list: Specific expertise, diagnostic precision, individualization of dosage or special equipment required for proper use (this precautions apply mainly in the context of chemotherapy with 5-fluorouracil, not for its use in HIV/AIDS).

tablet, 15 mg. EDL Reported shelf-life: 24 to 36 months.

Table 7. Sources and prices of antipneumocystosis and antitoxoplasmosis drugs.

ANTIPROTOZOALS <i>(incl. Ca-folate)</i>	Manuf. (1)		Indicative prices (USD, 1999) (2)						List Prices (3)	
	No./countries		Unit	MAX	MIN	MEDIAN	25th Perc./No.<		UK	Spain
Pentamidine										
inj, 300 mg (isetionate)	6	6	vial	64.04	7.48	25.66	12.04	2	55.14	11.66
Pyrimethamine										
tab, 25 mg	2	2	tab	0.010	0.005	0.008	0.006	1	0.12	0.06
Calcium folinate										
tab, 15 mg	6	6	tab	3.39	0.14	0.31	0.18	2	5.07	0.63

Explanatory notes to tables at the end of the document

Table 8. Drug costs associated with the treatment of toxoplasmosis.

TOXOPLASMOSIS. Treatment and duration (4)						Project estimates (25th percentile)		United Kingdom	
Drug	unit	Daily Dose	units/day	Days	Total units	Unit price (USD)	Total	Unit price (USD)	Total
Treatment									
Pyrimethamine	tab 25 mg	100 mg	4	42	168	0.006	1	0.12	20
plus Sulfadiazine	tab 500 mg	6 g	12	42	504	0.06	30	0.45	227
plus Calcium Folate	tab 15 mg	15 mg	1	42	42	0.18	8	5.06	213
							39		459
Secondary prophylaxis									
Pyrimethamine	tab 25 mg	25 mg	1	365	365	0.006	2	0.12	44
plus Sulfadiazine	tab 500 mg	3 g	6	365	2190	0.06	131	0.45	986
plus Sulfadiazine	tab 15 mg	15 mg	1	365	365	0.18	66	5.06	1847
							199		2876

Explanatory notes to tables at the end of the document

2. DRUGS USED IN HIV/AIDS RELATED MALIGNANCIES

2.1- CYTOTOXIC DRUGS

Bleomycin, Doxorubicin, Methotrexate, Vinblastine and Vincristine

Bleomycin

Generic bleomycin injection is available from manufacturers specialized in cytotoxics. Prices from different manufacturers vary widely. It is in the list of one international supplier.

Main use in HIV/AIDS: Kaposi's sarcoma. AIDS-related lymphoma.

Notes in 11th Model list: Specific expertise, diagnostic precision, individualization of dosage or special equipment required for proper use.

- **powder for injection, 15 mg (as sulfate) in vial.** EDL. Reported shelf-life: 18 to 24 months.

Doxorubicin

Doxorubicin is offered by the main companies that specialise in oncology drugs. While the powder for injection is the more usual form available, in developed countries the drug is offered also as a solution for injection. The lyophilised formulation is easier to store than the solution, which requires refrigeration.

Use in HIV/AIDS: Kaposi's sarcoma. AIDS-related lymphoma.

Notes in 11th Model list: Specific expertise, diagnostic precision, individualization of dosage or special equipment required for proper use.

- **powder for injection, 10 mg in vial.** EDL. Reported shelf-life: 18 to 36 months.
- **powder for injection, 50 mg in vial.** EDL. Reported shelf-life: 18 to 36 months.

Methotrexate

Methotrexate is widely available in the generic market, especially in the tablet form. The formulations included in the EDL are powder for injection 50 mg and tablets 2.5 mg. Generic manufacturers and international suppliers offer also the solution for injection, 2.5 mg/ml in 2-ml vial.

Use in HIV/AIDS: AIDS-related lymphoma.

Notes in 11th Model list: Specific expertise, diagnostic precision, individualization of dosage or special equipment required for proper use.

- **powder for injection, 50 mg (as sodium salt) in vial.** EDL. Reported shelf-life: 24 months.
- **injection, 25 mg (as sodium salt)/ml in 2-ml vial.** EDL (alternative formulation). Reported shelf-life: 24 to 36 months.
- **tablet, 2.5 mg.** EDL. Reported shelf-life: 24 to 36 months.

Vinblastine

The drug is available as powder for injection or solution for injection from various manufacturers. In addition, it is offered by international suppliers. Both formulations require refrigeration.

Use in HIV/AIDS: Kaposi's sarcoma.

Notes in 11th Model list: Specific expertise, diagnostic precision, individualization of dosage or special equipment required for proper use.

- **powder for injection, 10 mg (sulfate) in vial.** EDL. Indicated shelf-life: 18 to 36 months. REFRIGERATION REQUIRED.
- **injection, 1 mg (sulfate)/ml in 10-ml vial.** EDL (alternative formulation). Reported shelf-life: 18 to 36 months. REFRIGERATION REQUIRED.

Vincristine

As is the case of vinblastine, vincristine is available from generic manufacturers and international distributors. Two presentations are available, powder for injection and solution for injection. The powder for injection is listed in the Model EDL. Both must be kept refrigerated.

Use in HIV/AIDS: Kaposi's sarcoma. AIDS-related lymphoma.

Notes in 11th Model list: Specific expertise, diagnostic precision, individualization of dosage or special equipment required for proper use.

- **powder for injection, 1 mg (sulfate) in vial.** EDL. Reported shelf-life: 24 to 30 months. REFRIGERATION REQUIRED.

Table 9. Sources and prices of cytotoxic drugs.

Cytotoxics	Manuf. (1)		Indicative prices (USD, 1999) (2)						List Prices (3)	
	No./countries		Unit	MAX	MIN	MEDIAN	25th Perc./No.<		UK	Spain
Bleomycin										
inj, 15 mg in vial	7	7	vial	45.60	14.50	27.26	19.00	2	26.20	11.40
Doxorubicine HCl										
inj, 10 mg in vial	7	7	vial	14.52	2.52	8.38	4.25	2	30.11	6.17
Methotrexate										
inj, 50 mg in vial	5	5	vial	5.74	1.80	3.29	2.90	2	----	4.02
tab, 2.5 mg	7	7	tab	0.19	0.10	0.12	0.10	2	0.23	0.05
Vinblastine										
inj, 10 mg in vial	4	4	2-ml	18.87	6.50	14.37	9.43	1	22.76	5.57
Vincristine										
inj, 1 mg (sulfate) in vial	4	4	vial	4.08	1.15	3.38	2.54	1	----	6.84
inj, 5 mg (sulfate) in vial	2	2	vial	12.00	4.75	8.38	6.56	1	----	----

Explanatory notes to tables at the end of the document

Table 10. Drug costs associated with the treatment of Kaposi's sarcoma.

KAPOSI'S SARCOMA. Treatment and duration (5)						Project estimates (25th percentile)		United Kingdom	
Drug	unit	Daily Dose	units/day	Days	Total units	Unit price (USD)	Total	Unit price (USD)	Total
Treatment									
Bleomycin	inj 15 mg	15 mg/m ² (6 cycles)			12	19	228	26.15	314
plus Vincristine	inj 1mg	2 mg (6 cycles)			12	2.54	30	17.53 (a)	210
							258		524

Explanatory notes to tables at the end of the document

(a)- Price of solution for injection 1 mg/ml, 1 ml.

3. DRUGS USED IN PALLIATIVE CARE

3.1- OPIOD ANALGESICS

Codeine Phosphate, Methadone, Morphine, Pethidine

While opioid analgesics, including methadone for management of drug addiction, are essential components in palliative care for HIV/AIDS, the availability of drugs and range of formulations is limited in developing countries. This is partly due to regulatory constraints that affect the supply and usage of these drugs, and which affect specially countries where there is no local production.

International supply of opioid analgesics is limited to the more commonly used products (codeine tablets, morphine injection and pethidine injection). International suppliers and UNICEF include at least one of them in their product lists.

The drugs included in this section are all controlled substances under the Single Convention on Narcotic Drugs, 1961. Manufacturers require special authorization from the importing

country before an export license is granted, and due to regulatory constraints, batch samples are not available for evaluation.

Codeine

Use in HIV/AIDS: Treatment of mild to moderate pain, symptomatic relief of diarrhoea.

Notes in 10th Model list: Example of therapeutic group. Drug subject to international control.

- **tablet, 30 mg.** EDL. Reported shelf-life: 36 months

Methadone

Methadone is available in oral formulations (tablets and mixture) and in ampoules for injection. The more common form used in drug dependence are oral liquid formulations.

Use in HIV/AIDS: Management of opioid dependence.

- **Methadone, tablet, 5 mg.** Non-EDL
- **Methadone mixture DTF, 1 mg/ml.** Non-EDL

Morphine

Use in HIV/AIDS: Treatment of severe pain.

Notes in 10th Model list: Example of therapeutic group. Drug subject to international control.

- **injection, 10 mg (sulfate or hydrochloride) in 1-ml ampoule.** EDL. Indicated shelf-life: 24 to 36 months
- **oral solution, 10 mg (hydrochloride or sulfate)/5ml.** EDL
- **tablet, 10 mg (sulfate).** EDL
- Also: **oral solution, 5 mg (hydrochloride)/5 ml** (strength not in EDL), **sustained release tablet, 10 mg** (pharmaceutical form not in EDL).

Pethidine

Use in HIV/AIDS: Treatment severe pain.

Notes in 11th Model list: Example of therapeutic group. Complementary drug. Use when drugs in the main list cannot be made available. Drug subject to international control. In renal insufficiency, contraindicated or dosage adjustments necessary.

- **inj, 50 mg (hydrochloride) in 1-ml ampoule.** EDL. Reported shelf-life: 18 to 36 months

- **inj, 100 mg (hydrochloride) in 2-ml ampoule.** Dosage not in EDL. Reported shelf-life: 36 months.
- **tablet, 50 mg.** EDL. Reported shelf-life: 24 months
- **tablet, 100 mg.** EDL.

Table 11. Sources and prices of opioid analgesics .

ANALGESIC (OPIOID)	Manuf. (1)		Indicative prices (USD, 1999) (2)						List Prices (3)	
	No./countries		Unit	MAX	MIN	MEDIAN	25th Perc./No.<		UK	Spain
Codeine										
tab, 30 mg	6	6	tab	0.06	0.02	0.05	0.03	2	0.06	----
Methadone										
tab, 5 mg	----	----	----	----	----	----	----	----	0.10	0.07
Morphine										
inj, 10 mg in 1-ml amp	2	2	amp	0.44	0.26	0.35	0.31	1	1.06	0.18
tab, SR, 10 mg (sulfate)	1	1	SR tab	0.11	0.11	0.11	0.11	1	0.20	0.11
oral sol, 5 mg (HCl)/5 ml	1	1	450-ml	3.08	3.08	3.08	3.08	1	----	----
Pethidine										
inj, 50 mg/ml in 1-ml amp	4	4	amp	1.04	0.26	0.36	0.30	1	0.80	----
inj, 50 mg/ml in 2-ml amp	4	3	amp	0.39	0.27	0.31	0.27	1	0.76	0.49
tab, 50 mg	1	1	tab	0.13	0.13	0.13	0.13	1	0.15	----

Explanatory notes to tables at the end of the document

Notes to tables

(1)- Number of manufacturers that provided indicative prices and countries of origin.

(2)- As indicated by manufacturers. Prices are ex-works or FOB, and do not include freight, insurance or taxes. Range, median, 25th percentile and number of products with price equal to or below the 25th percentile are indicated. Exchange rates to USD vary (period between July and November 1999).

(3)- Spanish price is the manufacturers price as of July 1999, calculated from public prices indicated in Base de Datos del Medicamento del Consejo General de Colegios Farmaceuticos de España (www.cof.es). Prices indicated for the United Kingdom are those set by the NHS for reimbursement (British National Formulary 38, September 1999). Lowest price is indicated. Rates: 1 USD=162 ESP; 1 USD=0.623 GBP.

(4)- Examples of treatments. Source: Standard treatments and essential drugs for HIV-related conditions. 1997. WHO (DAP/97.9).

(5) The treatment indicated for Kaposi's Sarcoma is an example of BV therapy (Gill P, *et al.* 1990. American Journal of Clinical Oncology. 13(4), 315-9).

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UNICEF: www.unicef.org

WHO: www.who.org

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